Surgery for Acquired Cardiovascular Disease

ACD

Prospective randomized comparison of CarboMedics and St. Jude Medical bileaflet mechanical heart valve prostheses: Ten-year follow-up

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Objective: This is the final report of a randomized controlled trial comparing the performance of CarboMedics (CarboMedics Inc., Austin, Tex) and St. Jude Medical (St. Jude Medical Inc, St Paul, Minn) bileaflet mechanical heart valve prostheses 10 years after surgery.

Methods: Between 1992 and 1996, 485 patients undergoing mechanical heart valve replacement were randomized to receive CarboMedics (n = 234) or St. Jude Medical (n = 251) prostheses for aortic (n = 288), mitral (n = 160), or double (n = 37) valve replacements. Patients were followed annually to the end of 2004.

Results: Demographic, preoperative, and operative characteristics were similar between the 2 groups. The median follow-up was 10 years in both groups (CarboMedics 99% complete, St. Jude Medical 98% complete; 3879 patient-years of follow-up). Overall, 165 patients died, 25 of valve-related causes. Ten-year survivals were 66.4% (95% confidence interval: 59.6%-72.3%) and 64.7% (95% confidence interval: 58.0%-70.6%) in the CarboMedics and St. Jude Medical groups, respectively ($P = .94$). Freedom at 10 years from valve-related mortality was 95.0% (95% confidence interval: 90.8%-97.3%) in the CarboMedics group and 93.0% (95% confidence interval: 88.3%-95.9%) in the St. Jude Medical group. During follow-up, 34 patients had a thromboembolic event, 79 patients had at least 1 bleeding event, and 14 patients required reoperation. There were no significant differences between the groups with respect to freedom from complications ($P \geq .12$); freedom from thromboembolism at 10 years (CarboMedics: 91.5%, 95% confidence interval: 86.5%-94.7%; St. Jude Medical: 92.2%, 95% confidence interval: 87.5%-95.2%); freedom from bleeding events (CarboMedics: 83.0%, 95% confidence interval: 76.6%-87.8%; St. Jude Medical: 77.5%, 95% confidence interval: 71.1%-82.7%); and freedom from death or valve-related complication (CarboMedics: 51.6%, 95% confidence interval: 44.7%-58.0%; St. Jude Medical: 46.2%, 95% confidence interval: 39.7%-52.4%). Linearized rates per patient-year were 1.1% in the CarboMedics group and 0.8% in the St. Jude Medical group for thromboembolism; 2.3% in the CarboMedics group and 3.2% in the St. Jude Medical group for bleeding events; and 0.72% in the CarboMedics group and 0.47% in the St. Jude Medical group for nonstructural valve dysfunction. International normalized ratio values were similar between the 2 groups throughout the study period.

Conclusion: At 10 years, the clinical outcome was similar with respect to these 2 mechanical bileaflet prostheses.

Introduced in 1977, the St. Jude Medical (SJM) (St. Jude Medical Inc, St. Paul, Minn) mechanical bileaflet prosthesis was the first bileaflet pyrolytic carbon prosthesis. The CarboMedics (CM) (CarboMedics Inc., Austin, Tex) mechanical bileaflet prosthesis was introduced as an investigational prosthesis in 1986 and received Food and Drug Administration approval in 1993. Both prostheses have been widely used, and there are extensive observational studies describing their clinical performance.[1-4] There are differences in the design of the 2 prostheses,[5] which could conceivably confer differences in thromboembolic risk and other aspects of clinical performance. However, Akins[6] concluded that rates for valve-related complications were essentially comparable between CM and SJM valves, although data for the CM valve from a smaller study population did show a slightly higher rate of thromboembolic complications in the mitral position, despite adequate anticoagulation. This finding has been supported by others.[7,8] In contrast, Jamieson and colleagues[7,9] found no significant differences in thromboembolic tendency between the CM and SJM prostheses in isolated mitral valve replacement (MVR) or double valve replacement (DVR). A recent meta-analysis of these 2 prostheses found comparable thromboembolism and bleeding rates, but differing thrombosis rates (lower with the CM aortic valve and higher with the CM mitral valve compared with the corresponding SJM valves). However, whether the differences observed were of any clinical importance was doubtful.[10] Long-term randomized studies to evaluate experiences with these prostheses have been lacking to date, although an interim analysis of this study at 5 years has been presented.[11]

Although some argue that randomized controlled trials are not essential in evaluating prostheses, the conflicting and occasionally worrisome outcomes reported in observational studies make randomized controlled studies an important contribution to the assessment of the clinical performance of particular valve prostheses.

This is the second and final report of a randomized controlled trial comparing the clinical outcome of patients who received either CM or SJM standard mechanical heart valves implanted at a single institution with a median follow-up of 10 years.

Abbreviations and Acronyms

AVR = aortic valve replacement
CM = CarboMedics
DVR = double valve replacement
INR = international normalized ratio
MVR = mitral valve replacement
NYHA = New York Heart Association
SJM = St. Jude Medical
SMR = standardized mortality ratio

Materials and Methods

Patient Recruitment

From July 1992 to June 1996, patients scheduled to undergo mechanical heart valve replacement surgery at the Bristol Heart Institute under the care of a team of 5 consultant cardiac surgeons were recruited by individual consent into the study, which was approved by the local hospital research ethics committee. Exclusion criteria included inability to obtain informed consent, known follow-up difficulties, surgery to the ascending aorta, history of bleeding diathesis, blood dyscrasias, major neurologic disorders (eg, epilepsy), and long-term hemodialysis. Random assignment was by card allocation at time of surgery.

Surgery and Postoperative Management

All operations were performed through a median sternotomy with cardiopulmonary bypass and mild systemic hypothermia (28°C-32°C). Myocardial protection consisted of intermittent antegrade ± retrograde cold (6°C) St. Thomas crystalloid or blood cardioplegia. The prostheses used in both the CM and SJM groups were of standard design. Interrupted or continuous suturing technique was used at the discretion of the operating surgeon. All patients received postoperative subcutaneous heparin until the international normalized ratio (INR) was greater than 2 with warfarin administration. On discharge, anticoagulation was managed in the community by general medical practitioners or at local hospitals according to the British Society of Haematology guidelines.[12] For the initial part of the study, these guidelines recommended a target INR of 3.0 to 4.5 for all patients with mechanical heart valves. Subsequent revisions of this advice have acknowledged that modern bileaflet prostheses may be anticoagulated at a lower level.[13]

Clinical and Study Follow-up

Patients were seen at 6 weeks for a clinical review and thereafter referred to their cardiologist for annual review. Study follow-up was primarily by postal questionnaire sent to each patient on the anniversary of his or her operation. Patients were contacted directly only when clarification of details was necessary. The family practitioner and/or hospital cardiologist was contacted, and hospital health records were used where appropriate to clarify clinical events.

When a death occurred, the postmortem report was requested. The death registry of the UK Office of National Statistics was used to provide details of deaths that were otherwise unobtainable.

Adverse events, when reported, were categorized by a clinician blinded to valve type. Anticoagulation data (last 10 INR values) and drug dosages were obtained from the anticoagulant history booklet carried by the patient and filled out by the physician responsible for the patient's care. Data collection was terminated at the end of December 2004, the planned end of the study.

Statistical Analysis and Data Reporting

The original "Guidelines for Reporting Morbidity and Mortality after a Cardiac Valvular Operation"[14] and its subsequent revi-

sion[15] were followed for definitions of valve-related complications, analysis, and presentation of data and results. The data were collected using a standard proforma and stored in a computerized database. Continuous data are presented as a mean and standard deviation or median and interquartile range as appropriate, and categoric data are presented as a number and percentage. Event-free survival was estimated using the Kaplan–Meier method and compared across CM and SJM groups using the Wilcoxon test. Mortality estimates, including linearized rates of percentage events per patient-year, include in-hospital deaths. Age and gender standardized mortality ratios (SMRs) were calculated using UK Office of National Statistics mortality rates for England and Wales in 2001. Multiple logistic regression, adjusting for baseline New York Heart Association (NYHA), valve position, and follow-up year, was used to compare the proportion of patients in NYHA functional classes III/IV between the 2 study groups. Robust standard errors, clustered by patient, were used to take account of the non-independence between annual NYHA assessments from the same patient. Potential interactions were examined and retained if significant at the 5% level. The results are presented as odds ratios.

With respect to morbidity, significant bleeding events were those resulting in transfusion, hospitalization, or death, and thromboembolic events were any event, either transient or permanent, where there was clinical corroboration. Multiple events during follow-up were included in the calculation of linearized rates for thromboembolism and bleeding events. The composite end point of valve-related complications included (1) thromboembolic events, (2) bleeding events, (3) reoperation, and (4) death due to any cause. INR values are displayed graphically. Standard errors are adjusted to take account of the multiple INR readings per patient per year. The data were analyzed using Stata version 8.2. (Stata Corp, College Station, Tex).

Results

Patient Characteristics

During the recruitment period a total of 590 patients underwent mechanical prosthetic valve replacement. Of these 590 patients, 485 (82%) consented and were randomized and followed up (234 patients received a CM prosthetic valve, and 251 patients received an SJM prosthetic valve). Overall, 288 patients underwent aortic valve replacement (AVR), 160 patients underwent MVR, and 37 patients underwent DVR (Figure E1). The median ages were 63 years (interquartile range 55-68) in the CM group and 63 years (interquartile range 56-69) in the SJM group, and 45% of patients were female in both groups (Table E1). The majority of patients were admitted on a planned elective basis, with 83 patients (17%) listed for urgent valve replacement and 18 patients (4%) listed for emergency valve replacement. More patients were in NYHA class III/IV among those who underwent MVR (66%) and DVR (70%) than in those undergoing isolated AVR (48%,), but the NYHA class distribution was similar between the CM and SJM groups. Preoperative atrial fibrillation and anticoagulation therapy were also more prevalent among patients undergoing MVR or DVR (>55%) than in those undergoing AVR (<9%), and again there was no difference between the SJM and CM groups. The 2 groups were compared and found to be similar with respect to their baseline characteristics.[11]

Operative data describing suturing techniques, ischemic time, and cardiopulmonary bypass, as well as the cause of valve dysfunction, have been presented.[11] In patients undergoing AVR the most common cause was calcific, compared with a rheumatic cause in the MVR and DVR groups. No differences between the CM and SJM groups with respect to any operative variables or factors relating to additional procedures or the cause of valve dysfunction were found.

Patient Survival

The early (30-day) mortality was 5.2% (n = 25, CM 14, SJM 11, $P = .43$). A detailed description of the causes of early death is given in our 5-year interim report.[11] The median follow-up was 10 years (interquartile range 9-11 years) and was 99% and 98% complete for the CM and SJM groups, respectively. During the total of 3879 patient-years of follow-up (CM, 1897 patient-years; SJM, 1983 patient-years), there were 165 deaths (CM 81, SJM 84). The overall survival at 10 years was 66.4% in the CM group (95% confidence interval [CI] 59.6%-72.3%) and 64.7% in the SJM group (95% CI 58.0%-70.6%) ($P = .94$) (Figure 1, *A*). The death rate was 4.3% per patient-year (95% CI 3.4%-5.3%) in the CM group and 4.2% per patient-year (95% CI 3.4%-5.2%) in the SJM group. Postmortem diagnoses were available in 36% of cases (CM 37%, SJM 35%). In cases without a postmortem diagnosis, the cause of death was assigned by the clinical diagnosis. In 109 cases, death was due to cardiac causes, 25 of which were considered valve-related (CM 11, SJM 14). The specific causes of valve-related death are presented in Table 1. At 10 years, freedom from valve-related death was 95.0% in the CM group (95% CI 90.8%-97.3%) and 93.0% in the SJM group (95% CI 88.3%-95.9%) ($P = .58$).

SMRs were 1.99 (95% CI 1.55%-2.43%) in the CM group and 1.74 (95% CI 1.37%-2.11%) in the SJM group, indicating that the risk of death for study patients was higher than for those of the same age and gender in the general population. However, the SMRs for the CM and SJM groups were similar (ratio of SMRs [CM/SJM] = 1.15 [95% CI 0.83%-1.58%]).

Analysis by valve position showed that survival at 10 years differed significantly among the 3 valve positions ($P = .005$). Overall, survival was 72.1% after AVR, 54.4% after MVR, and 62.3% after DVR (see Figure 1 for a breakdown by prosthesis). Within each subgroup, no statistically significant difference between the 2 prostheses was found ($P \geq .53$) (Figure 1, *B-D*).

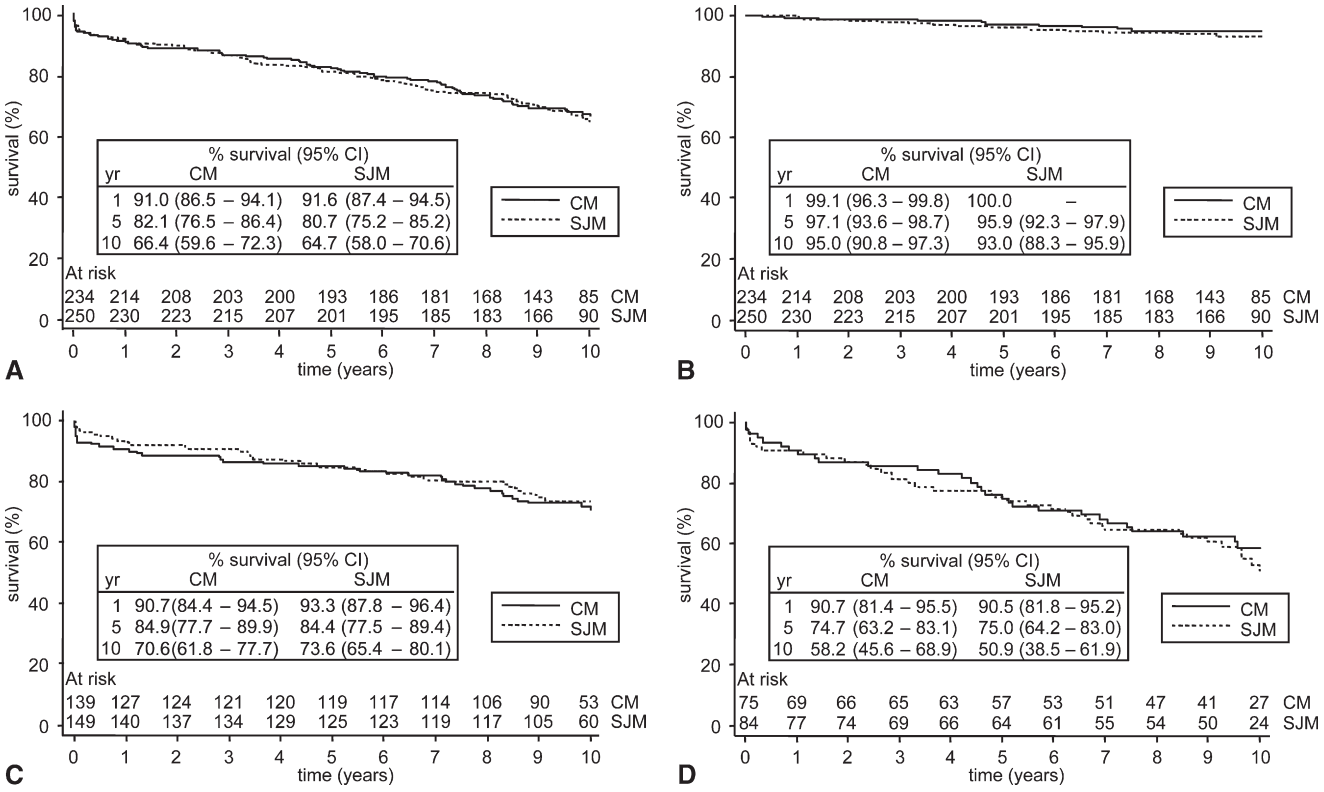

Figure 1. Kaplan–Meier plots: overall patient survival (A), freedom from valve-related death (B), and patient survival for AVR only (C) and MVR only (D). *CM*, CarboMedics; *SJM*, St. Jude Medical; *CI*, confidence interval; *AVR*, aortic valve replacement; *MVR*, mitral valve replacement.

Anticoagulation

For the assessment of anticoagulation status, 28,518 INR readings were available in 425 patients. The cumulative distribution of INR measurements, pooled over all patients and follow-up periods, by prosthesis and valve position is shown in Figure E2. No differences between the groups were found; the mean INR was 3.13 (standard error 0.023) in the CM group and 3.12 (standard error 0.025) in the SJM group. There were no obvious trends in anticoagulation during the 10 years of follow-up.

Valve-related Events

Thromboembolic events. Thirty-six (CM 20, SJM 16) thromboembolic events were reported during follow-up in 34 patients. Two patients in the CM group reported 2 events. Overall, 18 events (CM 10, SJM 8) were classified as transient, 5 events (CM 2, SJM 3) were classified as permanent without residual disability, and 13 events (CM 8, SJM 5) were classified as permanent with residual disability. A thromboembolic event occurred in 13 patients who underwent AVR, 19 patients who underwent MVR, and 2 patients who underwent DVR. The thromboembolic event rate was 1.1% per patient-year (95% CI 0.6%-1.6%) in the CM group and 0.8% per patient-year (95% CI 0.5%-1.3%) in the SJM group. Within the subgroup undergoing MVR, the thromboembolic event rate was 1.9% per patient-year (95% CI 1.0%-3.5%) in the CM group and 1.5% per patient-year (95% CI 0.7%-2.8%) in the SJM group.

At 10 years, 91.5% of patients (95% CI 86.5%-94.7%) in the CM group and 92.2% of patients (95% CI 87.5%-95.2%) in the SJM group were free of thromboembolism ($P = .63$, Figure 2). Thromboembolism-free survival after 10 years in relation to valve position was predictably higher in the aortic position at 94.8% (95% CI 91.1%-97%) compared with the mitral position at 85.5% (95% CI 77.7%-90.7%) ($P = .003$) (Figure 2).

Bleeding events. A total of 107 (CM 44, SJM 63) bleeding events were reported during follow-up in 79 patients (CM 32, SJM 47). Fifty-eight patients (CM 21, SJM 37) reported 1 event, 16 patients (CM 10, SJM 6) reported 2 events, 3 patients (CM 2, SJM 1) reported 3 events, and 2 patients (SJM group) reported 4 bleeding events. Overall, 89 events (CM 38, SJM 51) required hospital admission, 17 events (CM 6, SJM 11) included a blood transfusion, and

TABLE 1. Follow-up and mortality

Variable	All		AVR		MVR		DVR	
	CM	SJM	CM	SJM	CM	SJM	CM	SJM
Patients (No.)	234	251	139	149	75	85	20	17
Follow-up (mo)								
Median (IQR)	120 (108-132)	120 (108-120)	120 (108-132)	120 (108-132)	120 (108-132)	120 (108-132)	108 (107-132)	120 (108-120)
Maximum	145	144	144	144	145	144	144	144
Patient-y	1897	1983	1157	1241	573	617	167	125
Completion of follow-up (%)	99	98	99	98	99	99	100	100
Early mortality (<30 d, No.)	14	11	10	4	3	4	1	3
Overall mortality (No.)	81	84	41	39	34	38	6	7
Cardiac deaths	55	54	28	19	22	29	5	6
Valve-related	11	14	3	4	7	9	1	1
Hemorrhage	2	1	0	1	2	0	0	0
Nonstructural dysfunction	2	1	0	0	2	1	0	0
Prosthetic valve infection	1	4	1	0	0	4	0	0
Thromboembolism	3	3	1	1	1	1	1	1
Sudden unexpected/unexplained	3	5	1	2	2	3	0	0
Non-valve causes	44	40	25	15	15	20	4	5
Other causes	26	30	13	20	12	9	1	1

AVR, Aortic valve replacement; *MVR*, mitral valve replacement; *DVR*, double valve replacement; *IQR*, interquartile range; *CM*, CarboMedics (CarboMedics Inc, Austin, Tex); *SJM*, St. Jude Medical (St. Jude Medical Inc, St Paul, Minn).

1 event proved fatal (SJM group). One or more bleeding events occurred in 46 patients who underwent AVR, 23 patients who underwent MVR, and 10 patients who underwent DVR. The linearized bleeding event rate was 2.3% per patient-year (95% CI 1.7%-3.1%) in the CM group and 3.2% per patient-year (95% CI 2.4%-4.1%) in the SJM group. At 10 years of follow-up, 83.0% of patients (95% CI 76.6%-87.8%) in the CM group and 77.5% of patients (95% CI 71.1%-82.7%) in the SJM group were free of bleeding events ($P = .12$) (Figure 3).

Valve dysfunction and other valve-related complications. No cases of structural valve dysfunction or valve thrombosis were clinically detected. There were 8 cases of prosthetic valve endocarditis (CM 2, SJM 6), of which 4 were after AVR, 3 were after MVR, and 1 was after DVR. Of these patients, 5 underwent reoperation, all of whom survived. The linearized event rate was 0.11% per patient-year (95% CI 0.02%-0.42%) in the CM group and 0.30% per patient-year (95% CI 0.13%-0.67%) in the SJM group. Echocardiographic evidence of a paraprosthetic leak was recorded in 10 patients (CM 6, SJM 4) with no differences observed in relation to prosthesis type or valve position. In 5 cases, reoperation was indicated, and all 5 patients survived the reoperation. The 10-year event-free rates for nonstructural valve dysfunction were 92.5% (95% CI 87.0%-95.7%) (0.72% per patient-year) and 95.8% (95% CI 92.0%-97.8%) (0.47% per patient-year) for the CM and SJM groups, respectively ($P = .33$).

Valve-related complication-free survival. Overall, 248 patients had at least 1 complication (thromboembolic event, bleeding event, reoperation, or death from any cause) during follow-up. The complication-free survival at 10 years was similar for the 2 prostheses ($P = .37$). At 10 years, 51.6% of patients in the CM group (95% CI 44.7%-58.0%) and 46.2% of patients in the SJM group (95% CI 39.7%-52.4%) were free from valve-related complications (Figure 4, *A*). In contrast, a difference with valve position was seen, with the AVR group having a significantly higher event-free survival than the MVR and DVR groups (overall comparison, stratified by prosthesis, $P = .0006$, $P \leq .012$ for pairwise comparisons among AVR, MVR, and DVR groups) (Figure 4, *B*). At 10 years the event-free survival in the AVR group was 56.7% (95% CI 50.6%-64.2%) compared with 37.0% (95% CI 29.1%-44.9%) in the MVR group and 37.5% (95% CI 22.2%-52.8%) in the DVR group.

New York Heart Association Functional Class

The improvement in symptoms after valve replacement is clearly shown by the changes observed in the NYHA class over the study period, as illustrated in Figure 5. Overall, 55.9% of patients were in functional class III/IV before their operation. One year later, this had decreased to 11.9% of patients in NYHA class III/IV, increasing to 19.8% at 3 years and 20.4% at 10 years (Table E2).

There was evidence to suggest that proportionally fewer patients in the CM group were in NYHA class III/IV

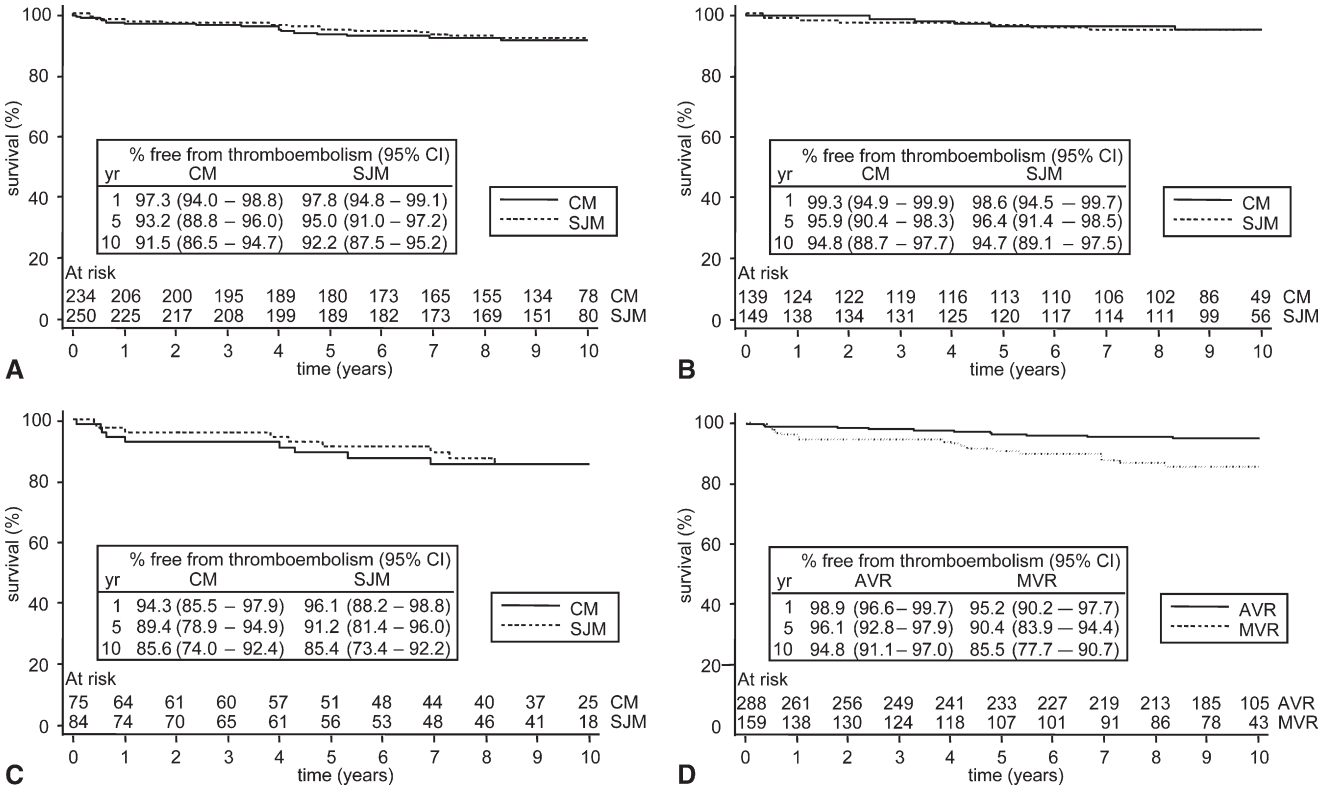

Figure 2. Kaplan–Meier plots: freedom from thromboembolism for all study patients (A), for AVR only (B), for MVR only (C), and by position of valve replacement (D). Abbreviation definitions as in Figure 1.

throughout the 10-year follow-up period compared with the SJM group odds ratio ([CM/SJM] = 0.69 [95% CI 0.48%-0.99%, $P = .05$]). The proportion of patients with poor functional status also differed by valve position ($P = .006$). Significantly fewer patients who underwent AVR were in NYHA class III/IV compared with the MVR and DVR groups, which were similar ($P = .72$).

Discussion

In this prospective randomized comparison of the SJM and CM mechanical bileaflet prostheses at 10 years, there was no difference in survival or any of the other commonly observed indices of morbidity after heart valve replacement operations: bleeding, thromboembolism, and prosthetic valve dysfunction.

The strengths of this study were that it was prospective and randomized and to our knowledge remains the only randomized controlled trial of these 2 heart valves. Although our randomization was simplistic by today's standards,[16] careful scrutiny of our study groups revealed no apparent differences with respect to any important variables. In addition, follow-up information was collected on an annual basis in a consistent manner by the same observers during the 12-year study period.

However, we must question to what extent our finding of no difference in the clinical performance of these 2 prostheses can be considered a definitive conclusion and to what extent this outcome may have been predictable based on the study size and duration. Akins[17] calculated in his learned discussion of our interim report that to definitively rule out any difference in performance between these 2 prostheses, taking into account the published ranges of complications, would require some 10,000 patient-years of follow-up with a study size of perhaps 1400 patients in each group. We therefore must consider this study an important further contribution to the information already available on the clinical performance of these heart valves and accept that the power of the study means it cannot conclusively be considered to demonstrate equivalent clinical performance.

In the study as a whole, we found that survival after AVR (72.1%) was better than after MVR (54.4%) or DVR (62.3%). These differences were more apparent when overall survival and valve-related complications were consid-

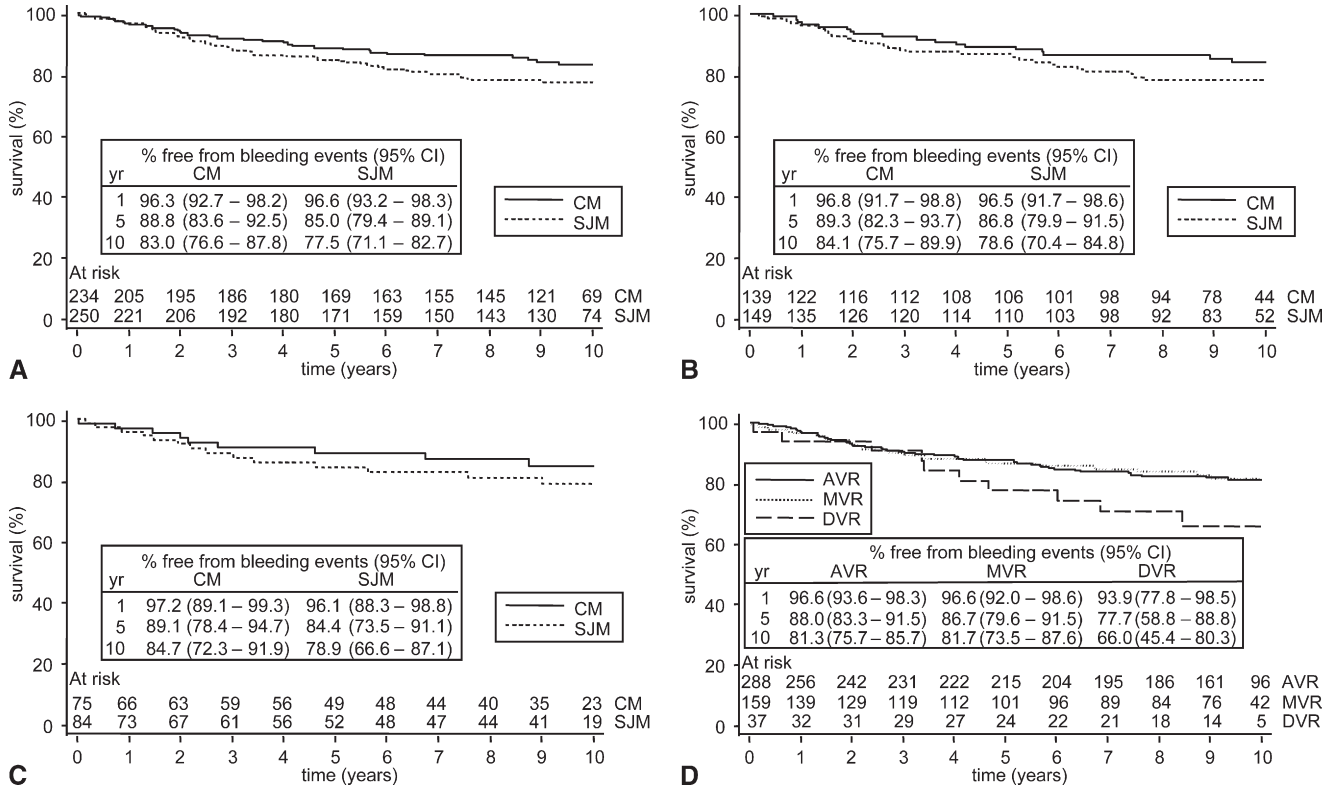

Figure 3. Kaplan-Meier plots: bleeding event-free survival for all study patients (A), for AVR only (B), for MVR only (C), and by position of valve replacement (D). Abbreviation definitions as in Figure 1.

ered. For this combined end point, survival after AVR was significantly higher than after both MVR and DVR ($P \leq .012$). This has been a common but not entirely consistent finding in studies after mechanical valve replacement, and we know that late survival is as much a function of the risk profile of the starting population as a reflection of prosthetic valve function. Nevertheless, the late survival and freedom from clinical events of patients after prosthetic MVR or

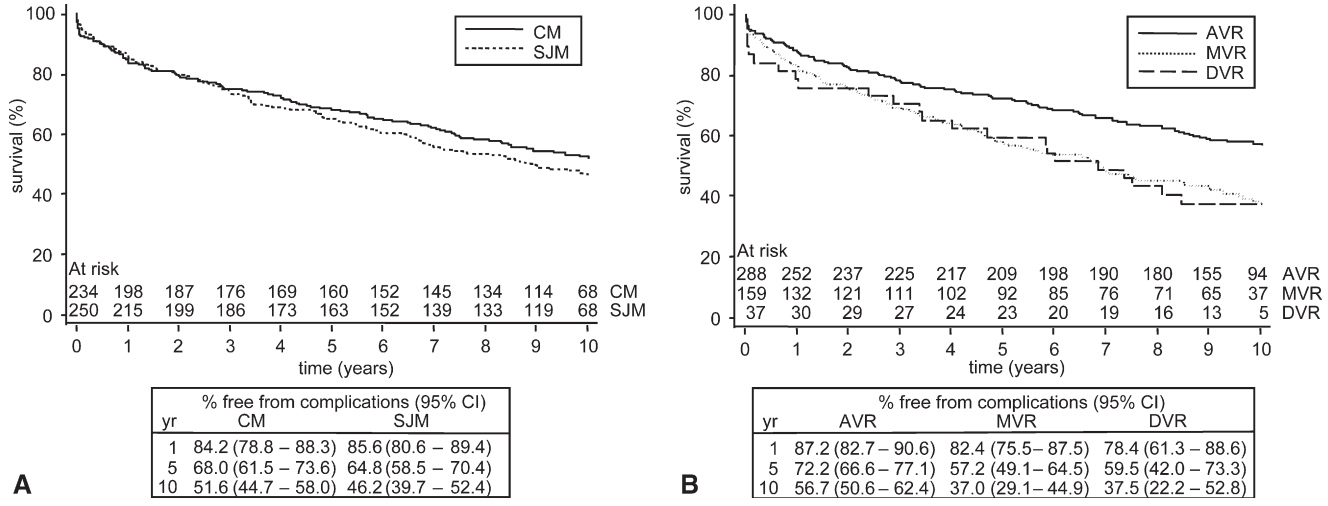

Figure 4. Complication-free survival by study group (A) and position of valve replacement (B). Abbreviation definitions as in Figure 1.

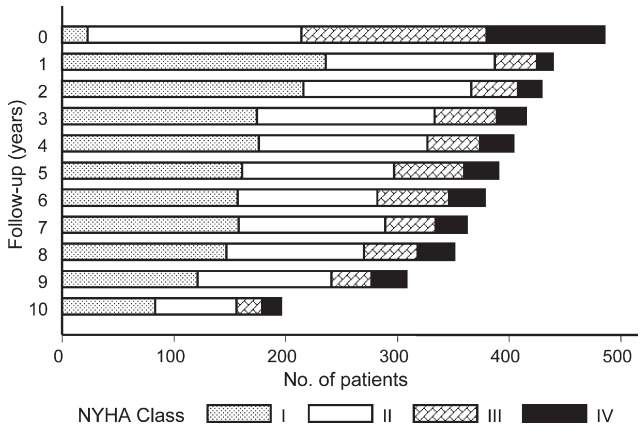

Figure 5. NYHA class by year of follow-up. *NYHA,* New York Heart Association.

DVR were disappointing and further support the application of mitral valve repair whenever possible.

The only difference in outcome we identified was a suggested difference in NYHA class during follow-up, with fewer patients in the CM group in NYHA class III/IV. This difference did not seem to reflect preoperative status, which was similar in the 2 groups. Echocardiographic analysis of left ventricular function may have been helpful in clarifying whether there were any differences in left ventricular function between the 2 groups, but this was not part of the study.

The rates of thromboembolism and bleeding are at the lower end of those recorded for these prostheses and consistent with previous observations.[6] In particular, despite the relatively small sample size there was no evidence of an increased thromboembolic risk associated with the CM mitral valve. With reference to the anticoagulation data, it is interesting that there was no difference in the management of these mechanical prostheses with respect to the position or type of prosthesis. Despite this study being conducted during the 1990s and early 2000s, with increasing understanding of prosthesis-specific anticoagulation, we found little evidence of any adaptation of the anticoagulation to the lower demands of (1) bileaflet prostheses and (2) prostheses in the aortic position. This may simply represent the rather crude management of anticoagulation in the community.

To improve outcome for our patients, we must aim to lower the levels of anticoagulation to reduce bleeding events without increasing the thromboembolic rate, which has been shown to be effective.[18] In addition, early institution of INR self-management can allow close control of prosthesis-specific anticoagulation and consequently low thromboembolic (0.21%/patient-year) and bleeding rates (0.56%/patient-year).[19]

It is at this point customary to suggest further possible research to elucidate further the problem under study. A study with more power would require a multicenter design with a large sample size. However, the increasing prevalence of mitral repair and the elderly surgical population dictating implantation of biological valves make this less and less likely. It is probably far more realistic to acknowledge that increasing information from observational studies and this randomized study provide an extensive basis on which to base a reasoned hypothesis that there is little to choose with respect to clinical performance between these 2 bileaflet prostheses.

We thank our surgical colleagues for their expertise in implanting the valves.

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Discussion

Dr von Segesser *(Lausanne, Switzerland)*. I congratulate Dr Bryan and Prof Angelini's group for this nice study that gives answers to some questions that have been around for many years, namely, whether there is a difference between the 2 types of valves. This brings me to the first question.

In the 1990s there have been at least a half a dozen design iterations between different CarboMedics and St. Jude valve designs. Can you specify the type of valve that was used in your study?

Dr Bryan. All of these valves were standard St. Jude Medical and CarboMedics prostheses.

Dr von Segesser. There seemed to be a slight difference with regard to thromboembolism between CarboMedics and St. Jude valves, not when you look at the single valve replacements but at the double valve replacements. Can you comment on that?

Dr Bryan. None of these differences attained anything like statistical significance. The number of thromboembolic events in the double valve group was very low, really, but even so, it didn't attain statistical significance, and the confidence limits widely overlapped.

Dr von Segesser. There appears to be, at least graphically, a difference with regard to bleeding between the St. Jude Medical and CarboMedics valves. After 10 years of follow-up you have about 77% bleeding-free survival for St. Jude Medical versus 83% for CarboMedics. If we look at a simple test like Fisher's exact, it comes up to about a 0.7 1-sided *P* value. I do not claim that this is significant, but did you explore this any further?

Dr Bryan. This is an unusual article for me, because actually the other 2 authors are both statistical advisors. So it is the first study I have been involved with 2 statistical advisors and not 1, and perhaps that is a reflection of the statistical nature of these kind of analyses. I am told that there are no differences in relation to the bleeding events, and, again, I haven't presented *P* values on the slides because my advisors tell me that when the confidence limits overlap widely, it is not necessary.

Dr von Segesser. I agree that testwise there may not appear to be a difference, but graphically it seemed to be impressive. I wonder if you have an explanation why there was so much more bleeding in the St. Jude Medical group?

Dr Bryan. I think all I can say is although it might appear different, if it is not statistically significant, then we have to accept that it is not different.

Dr von Segesser. I would dare not to agree. Absence of proof is no proof of absence.

I have a final question. Did you have any objective measurement for valve performance between the 2 groups?

Dr Bryan. No, we did not. There were no echocardiographic data.

Dr K. Rasheed *(Islamabad, Pakistan)*. Congratulations on this impressive article and the quality of the presentation.

Regarding such a low rate of thromboembolism both in patients with single valves and double valves, would you tell us what INR you were maintaining for single and double valve replacements? Thank you.

Dr Bryan. With reference to the thromboembolic rate, as we all know from observational studies, there is a wealth of information in relation to these 2 valves, and the thromboembolic rate that we have recorded fits perhaps toward the lower end of those recorded in the literature, but it certainly is not the lowest.

In terms of the anticoagulation, in our country, anticoagulation is essentially community monitored; we cover a wide geographic area. So the guidelines that are instituted really are general guidelines that are decided by the British Society of Hematology. At the start of this study period, the guidelines for mechanical prosthetic valves was that the INR should be maintained for all valve models in all valve positions in a range from 3 to 4.5. This was modified in 1997 to indicate that for modern prostheses this should be adjusted. One of the reasons why I presented some of the anticoagulation data, which we have a wealth, is that actually there is little evidence of penetration of the concepts that have been brought to our attention by people, such as Eric Butchart, that we should be anticoagulating in a prosthesis-specific manner, and certainly in our population there was no evidence of this.

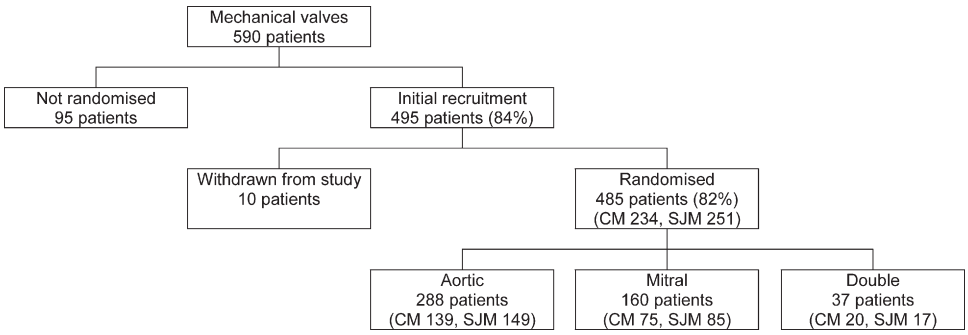

Figure E1. Flow chart showing study recruitment and randomization. *CM*, CarboMedics; *SJM*, St. Jude Medical.

TABLE E1. Baseline patient characteristics

	All		AVR		MVR		DVR	
Variable	**CM**	**SJM**	**CM**	**SJM**	**CM**	**SJM**	**CM**	**SJM**
Patients (No.)	234	251	139	149	75	85	20	17
Age (y, median [IQR])	63 (55-68)	63 (56-69)	63 (54-68)	64 (55-69)	63 (56-68)	63 (58-69)	63.5 (53-69.5)	61 (49-68)
Male (%)	55	55	65	67	41	35	35	47
Previous myocardial infarction (%)	12	10	10	11	17	9	5	6
Previous heart surgery (%)	21	24	13	13	29	41	40	35
Atrial fibrillation (%)	31‡	32†	7†	9*	65	65*	63*	59
History of thromboembolism (%)	9*	13	5*	9	16	21	15	6
Anticoagulation (%)	28*	28	9*	5	52	64	70	53
NYHA functional class (%)								
I	4	5	5	7	4	2	0	6
II	37	41	44	48	25	35	35	18
III	33	35	29	30	43	42	25	47
IV	25	18	22	16	28	20	40	29
Coronary artery disease (%)	29	27	30	28	32	28	10	18
Valve size								
Aortic (median [IQR])			23 (21-25)	23 (21-25)			21 (20-23)	21 (21-23)
≤19 mm (%)			16	9			25	19
21 mm (%)			21	33			35	44
≥23 mm (%)			63	58			40	37
Mitral (median [IQR])					29 (29-31)	29 (29-31)	29 (27-31)	29 (29-31)
≤27 mm (%)					23	14	40	6
29 mm (%)					31	38	30	53
≥31 mm (%)					46	48	30	41

AVR, Aortic valve replacement; *MVR*, mitral valve replacement; *DVR*, double valve replacement; *CM*, CarboMedics; *SJM*, St. Jude Medical; *IQR*, interquartile range; *NYHA*, New York Heart Association. One patient with DVR in the SJM group had a tricuspid valve (31 mm). *Missing data for 1 patient. †Missing data for 2 patients. ‡Missing data for 3 patients.

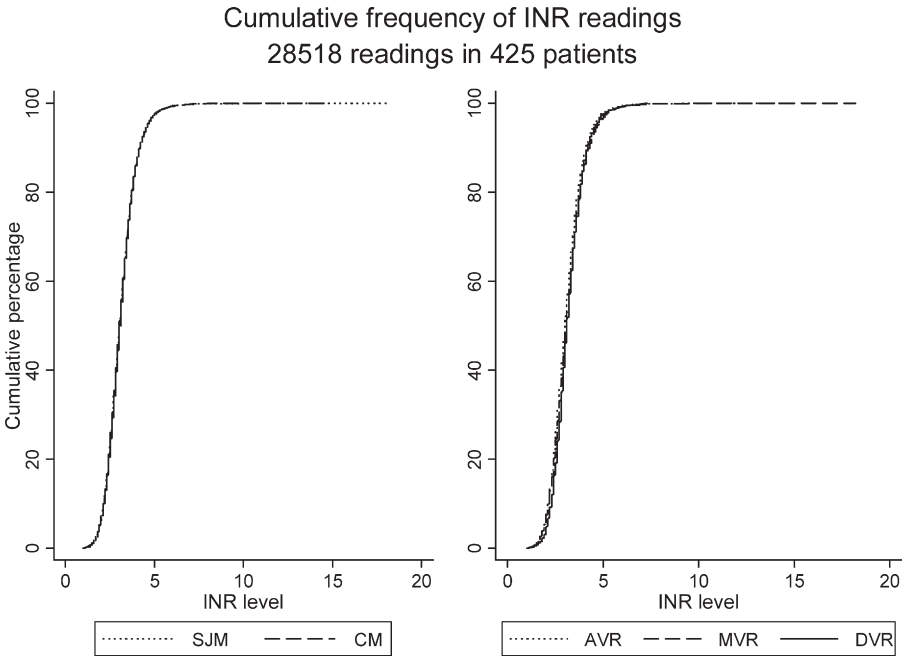

Figure E2. Anticoagulation control. ***INR***, **international normalized ratio;** ***SJM***, **St. Jude Medical;** ***CM***, **CarboMedics;** ***AVR***, **aortic valve replacement;** ***MVR***, **mitral valve replacement;** ***DVR***, **double valve replacement.**

TABLE E2. New York Heart Association functional class: Baseline and annual follow-up to 10 years

	CarboMedics					St. Jude Medical				
Year	I	II	III	IV	Total (100%)	I	II	III	IV	Total (100%)
0 (preop)	10 (4%)	87 (37%)	78 (33%)	59 (25%)	234	13 (5%)	104 (41%)	88 (35%)	46 (18%)	251
1	120 (57%)	68 (32%)	20 (9%)	4 (2%)	212	116 (51%)	83 (37%)	18 (8%)	10 (4%)	227
2	115 (56%)	65 (32%)	19 (9%)	7 (3%)	206	101 (45%)	85 (38%)	23 (10%)	14 (6%)	223
3	96 (48%)	73 (36%)	20 (10%)	12 (6%)	201	78 (36%)	86 (40%)	36 (17%)	14 (7%)	214
4	94 (47%)	75 (38%)	17 (9%)	12 (6%)	198	82 (40%)	76 (37%)	30 (15%)	18 (9%)	206
5	80 (42%)	69 (36%)	30 (16%)	12 (6%)	191	81 (41%)	67 (34%)	33 (17%)	18 (9%)	199
6	81 (44%)	64 (35%)	26 (14%)	14 (8%)	185	76 (39%)	61 (32%)	38 (20%)	18 (9%)	193
7	76 (43%)	70 (39%)	24 (13%)	8 (4%)	178	82 (45%)	61 (33%)	21 (11%)	20 (11%)	184
8	71 (42%)	64 (38%)	21 (12%)	13 (8%)	169	76 (42%)	59 (32%)	27 (15%)	20 (11%)	182
9	55 (38%)	60 (42%)	16 (11%)	12 (8%)	143	66 (40%)	60 (36%)	20 (12%)	19 (12%)	165
10†	37 (38%)	43 (44%)	11 (11%)	6 (6%)	97	46 (46%)	30 (30%)	12 (12%)	11 (11%)	99

*Not all percentages sum to exactly 100% because of rounding. †Follow-up ceased in December 2004, which meant that not all patients had the potential to achieve 10-year follow-up.